ERYTHROPOIESIS STEMULATING AGENTS (ESA) IN TREATMENT OF ANAEMIA IN CHRONIC KIDNEY DISEASE(CKD)

By

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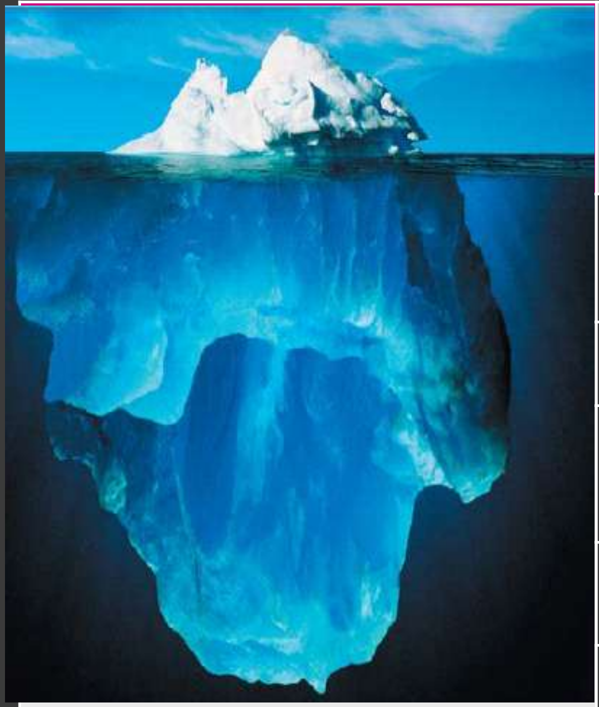
CKD is Highly Prevalent with Majority in Early Stages

Prevalence of CKD by Stage



CKD stage	Prevalence*	Prevalence of Anemia Hb<12gm/dl
ESRD or Stage 5	0.04	90%%
Stage 4	0.17	53.6%
Stage 3	4.2	26.7%
Stage 2	15.4	
Stage 1	5.3	

Data from the NeoERICA database (n=41,296 patients)

*** Prevalence as % UK population**

Adapted from Stevens *et al*. EDTA-ERA Lisbon 2004

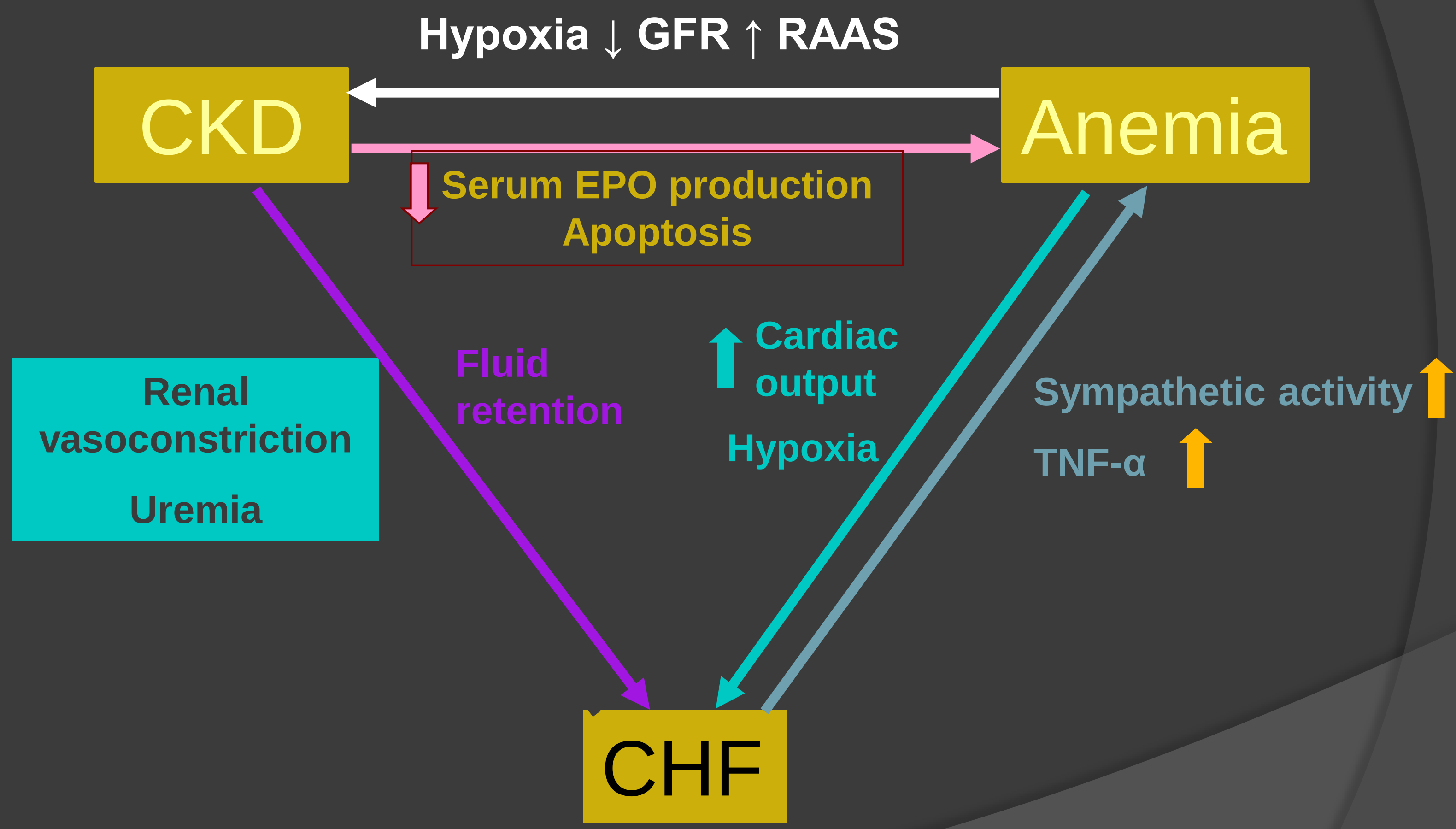
Anemia is a serious problem

- Decreased tissue oxygen delivery and utilization
- Increased cardiac output
- Ventricular hypertrophy
- Cardiac enlargement
- Angina pectoris
- Congestive heart failure
- Reduced quality of life

- Decreased cognition and mental acuity
- Altered menstrual cycles
- Decreased sexual function
- Impaired immune responsiveness
- Growth retardation
- Decreased intellectual performance
- Poor patient rehabilitation

Decreased survival

The Cardio-Renal Anemia Syndrome *A vicious circle*

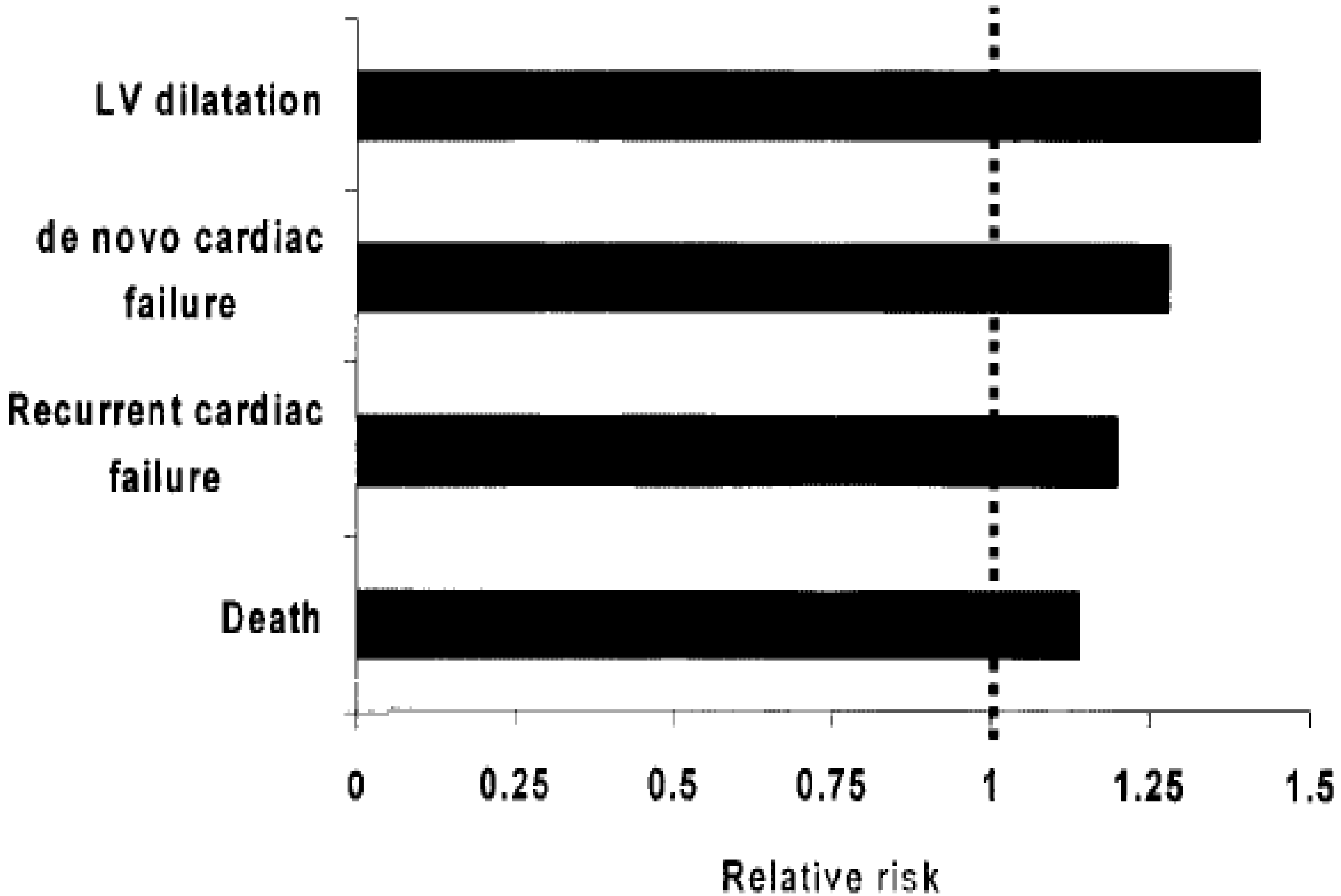


CHF=congestive heart failure

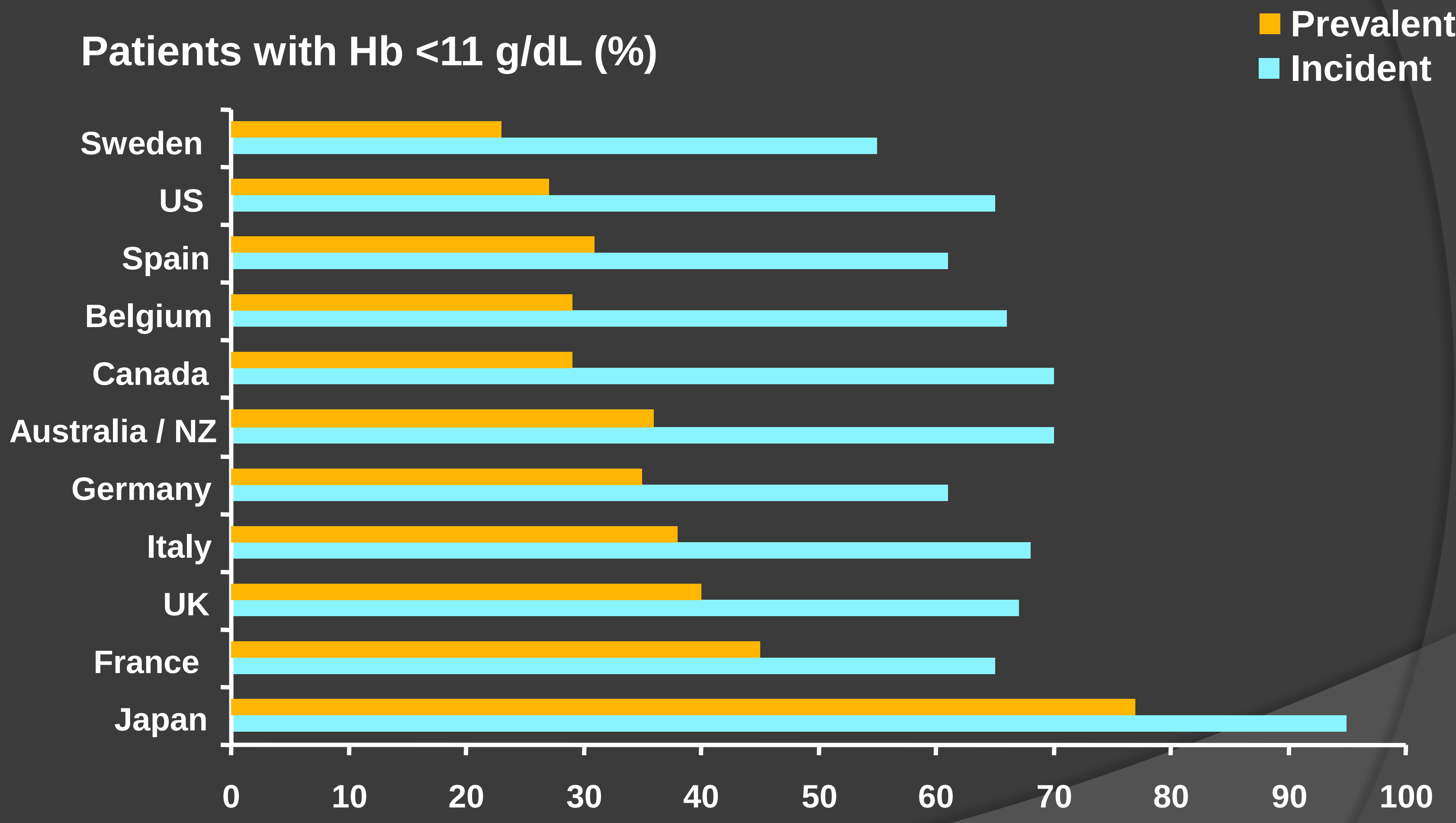
Adapted from Silverberg et al. *Kidney Int.* 2003;64(Suppl 86):S40-S47

Foley, et al. Am J Kidney Dis, 1996.

Anaemia in CRD

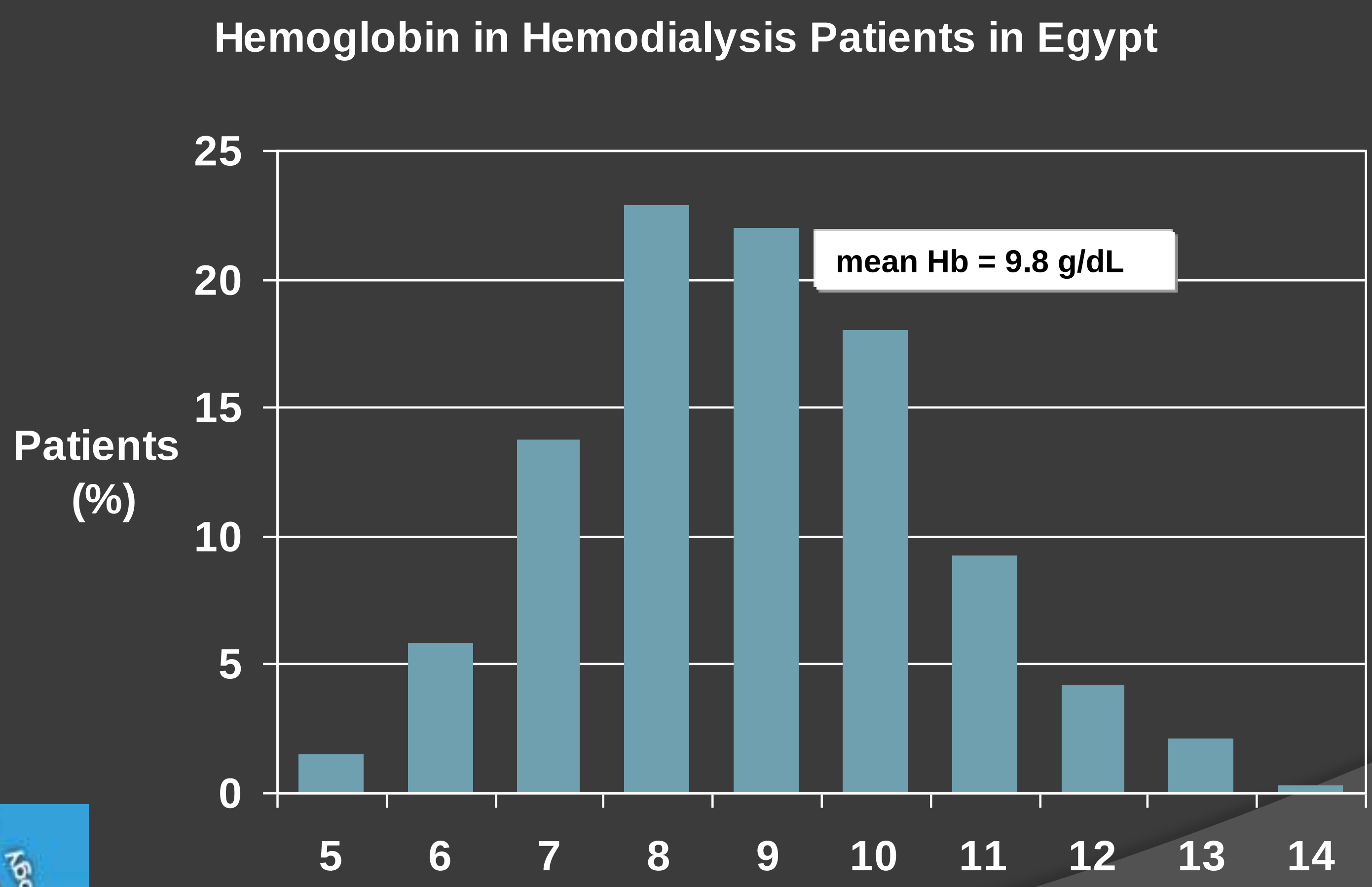


Challenges in Anemia Management



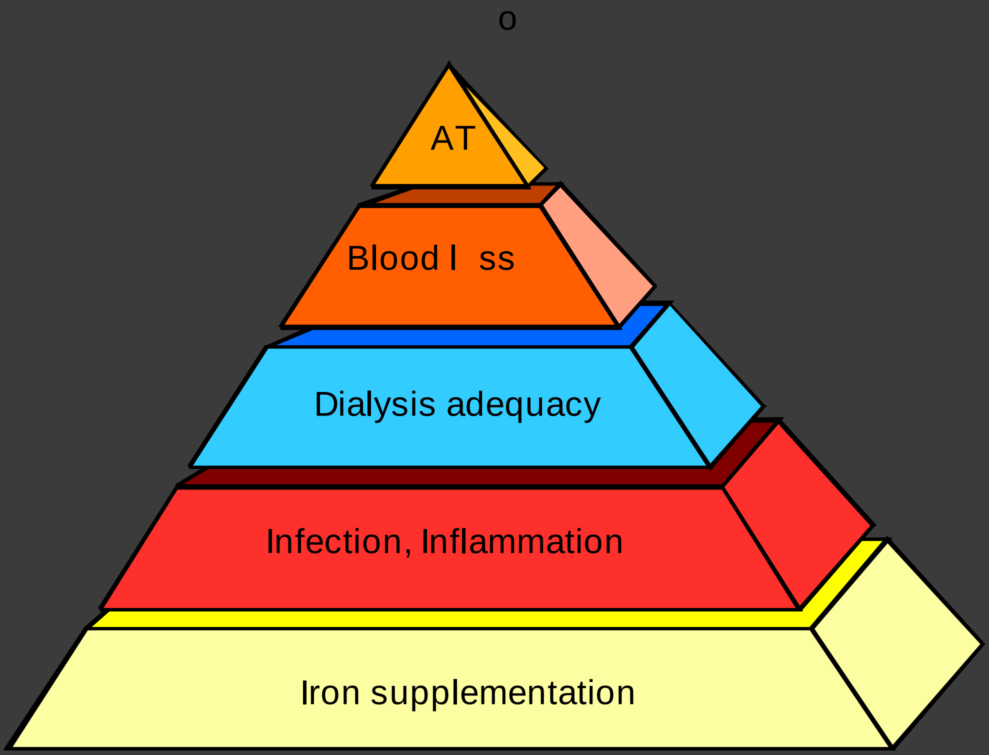
Locatelli et al. *Am J Kidney Dis.* 2004;44(Suppl 3):27-33
Pisoni et al. *Am J Kidney Dis.* 2004;44:94-111

Anemia among Egyption HD patients

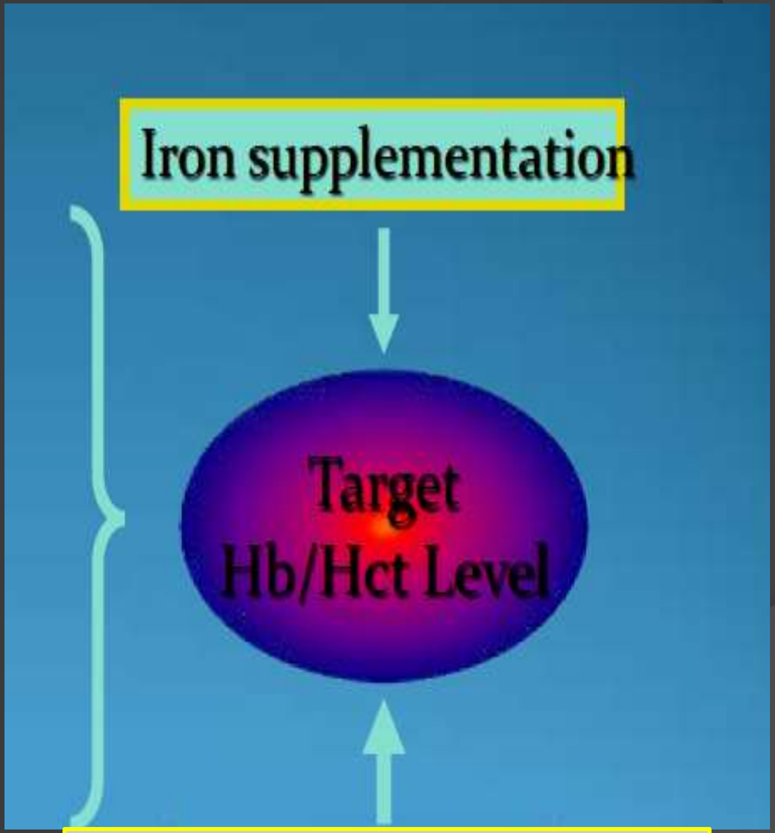


Treatment of Anemia

Factors influencing anemia treatment



AT = Adjuvant therapy



ESAs therapy

ERYTHROPOIETIN: FIRST STEPS

- **1906 Carnot - De Flandre postulated an humoral factor "hemopoietine" that regulates red blood production**
- **1957 Jacobson: kidney is the primary site of EPO production**
- **1977 Miyake: purification of human erythropoietin**
- **1985 Lin et al. - Jacobs et al.: cloning and expression of the human erythropoietin gene**
- **1988 Koury: peritubular interstitial cell in the kidney are the renal cells that produce EPO**

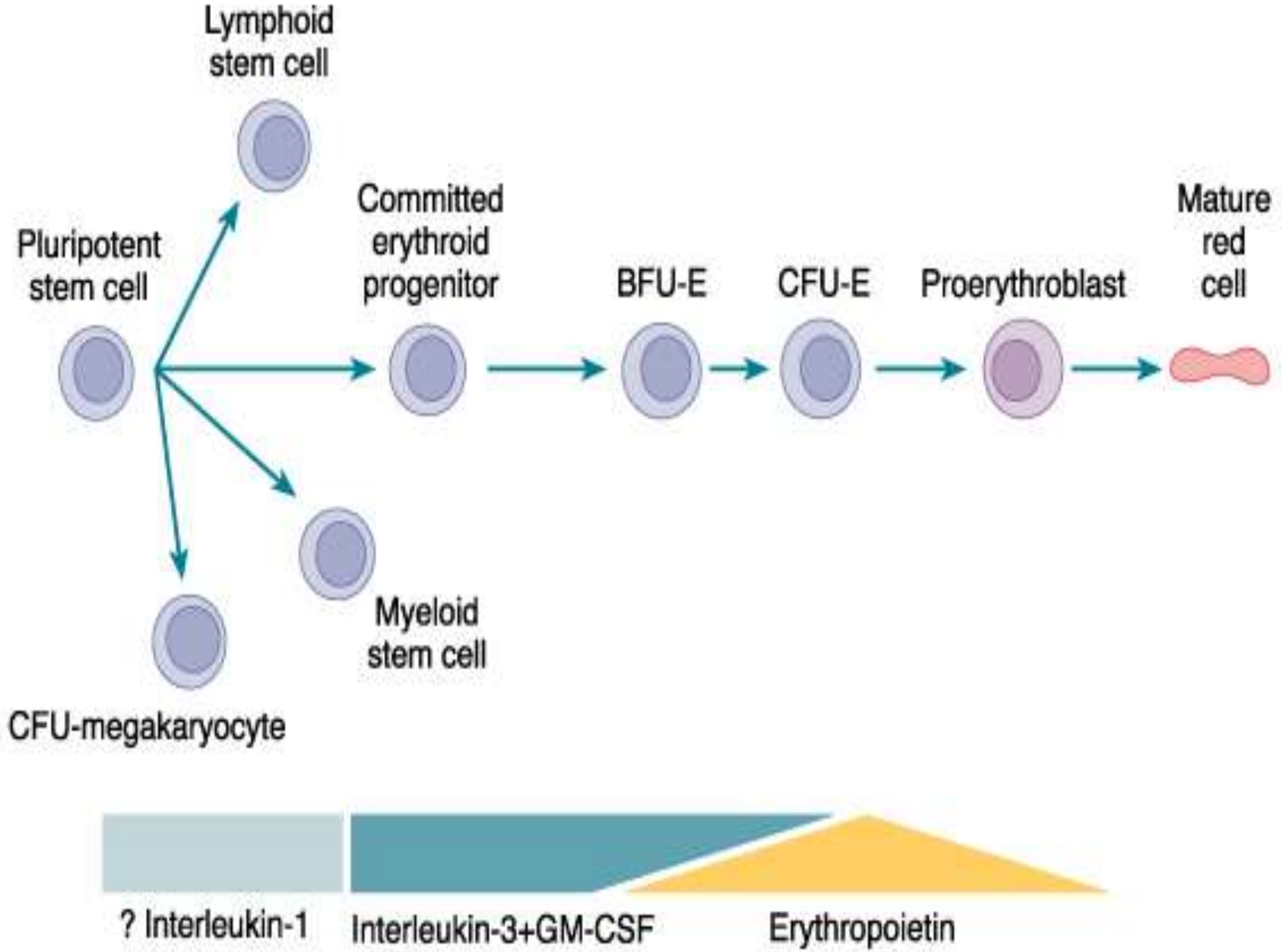
Epoetin alfa was approved by:

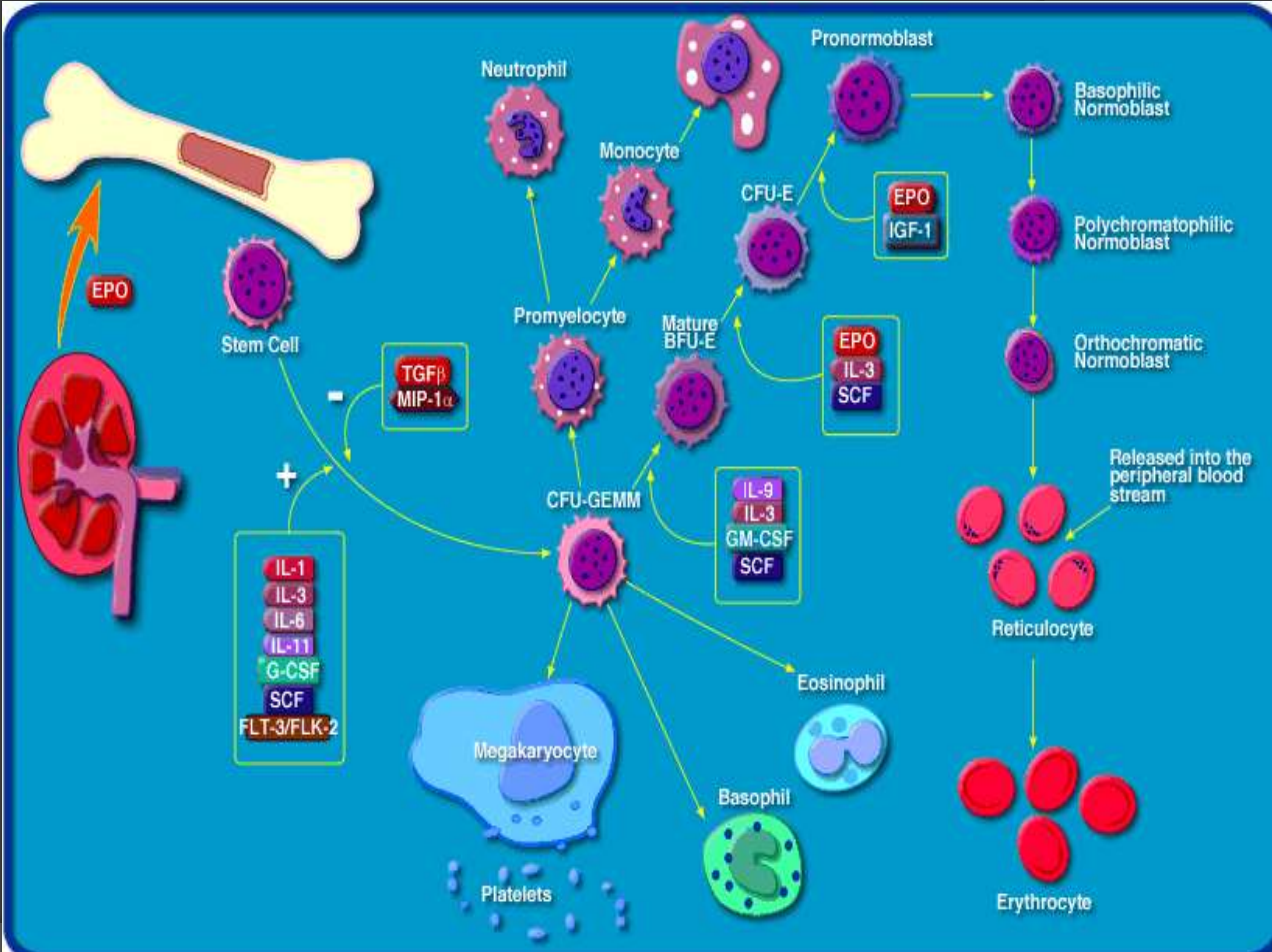
- The European Medicines Agency (EMEA) in 1988.
- The U.S. Food and Drug Administration (FDA) in 1989.

For the treatment of anemia related to chronic renal failure.

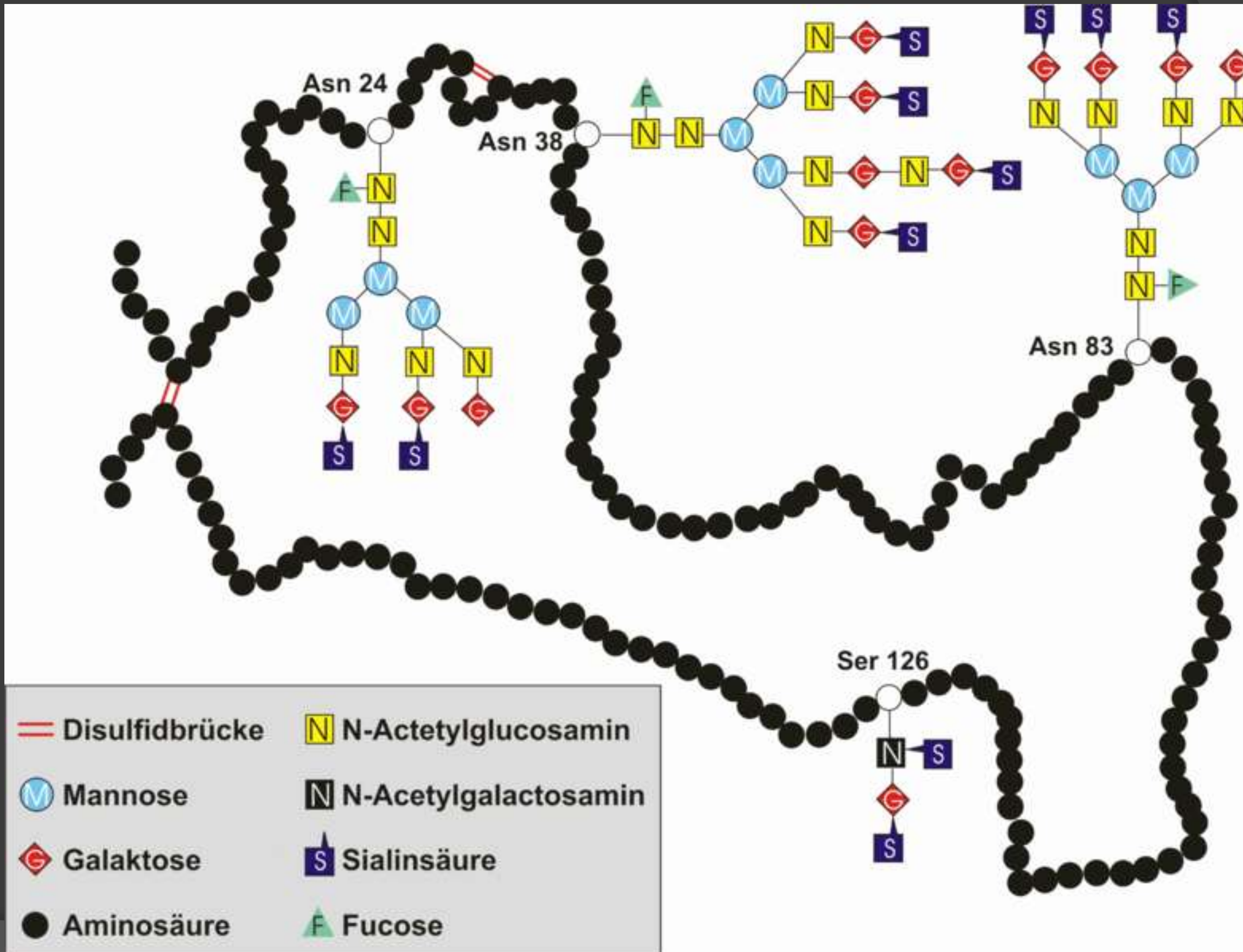
EPO Action

- EPO is needed for erythroid proliferation and differentiation.
- It acts synergistically with other cytokines on bone marrow colony-forming unit– erythroid cells to cause maturation and proliferation at the normoblast stage of erythroid cell development .
- Its absence results in a higher rate of apoptosis of cells committed to the erythroid line.
- The use of rHuEPO raises levels of hemoglobin (Hb), reducing transfusion requirements and improving quality of life.


Lymphoid stem cell
Pluripotent stem cell
Committed erythroid progenitor
BFU-E
CFU-E
Proerythroblast
Mature red cell
Myeloid stem cell
CFU-megakaryocyte
? Interleukin-1
Interleukin-3+GM-CSF
Erythropoietin

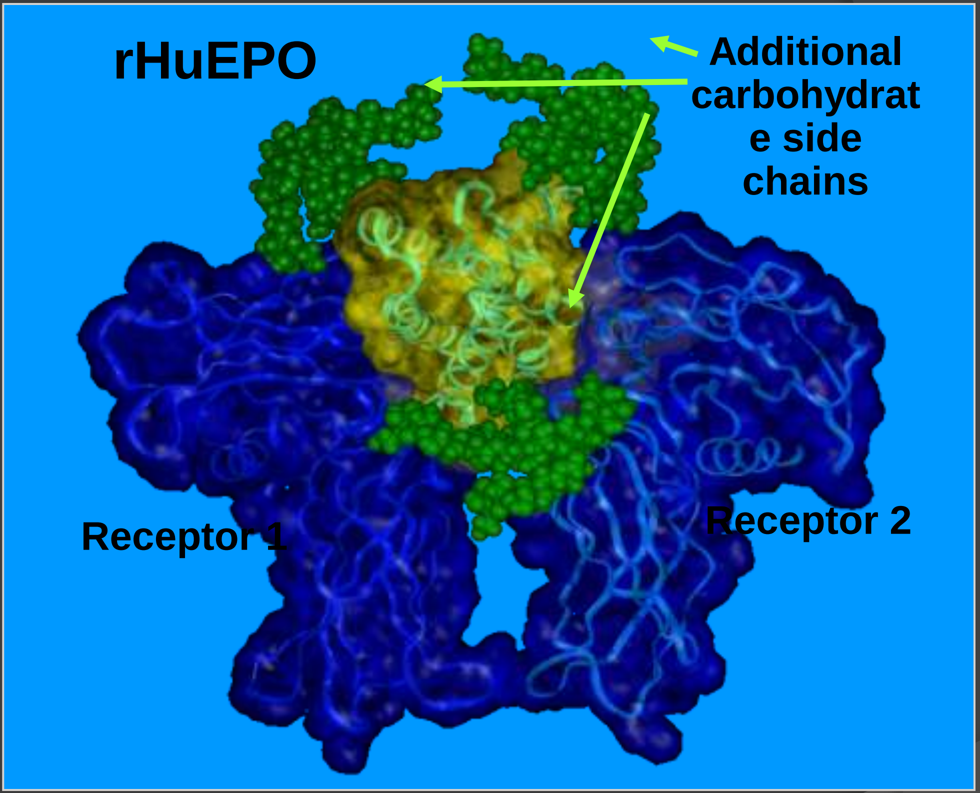

EPO
Stem Cell
Neutrophil
Monocyte
Promyelocyte
Pronormoblast
CFU-E
EPO
IGF-1
Mature BFU-E
EPO
IL-3
SCF
Basophilic Normoblast
Polychromatophilic Normoblast
Orthochromatic Normoblast
-
TGFβ
MIP-1α
+
IL-1
IL-3
IL-6
IL-11
G-CSF
SCF
FLT-3/FLK-2
CFU-GEMM
IL-9
IL-3
GM-CSF
SCF
Released into the peripheral blood stream
Reticulocyte
Megakaryocyte
Platelets
Eosinophil
Basophil
Erythrocyte

Erythropoietin is a large peptide (or small protein) comprising 165 amino acids with a large number of attached carbohydrate residues (it is 30% glycosylated).

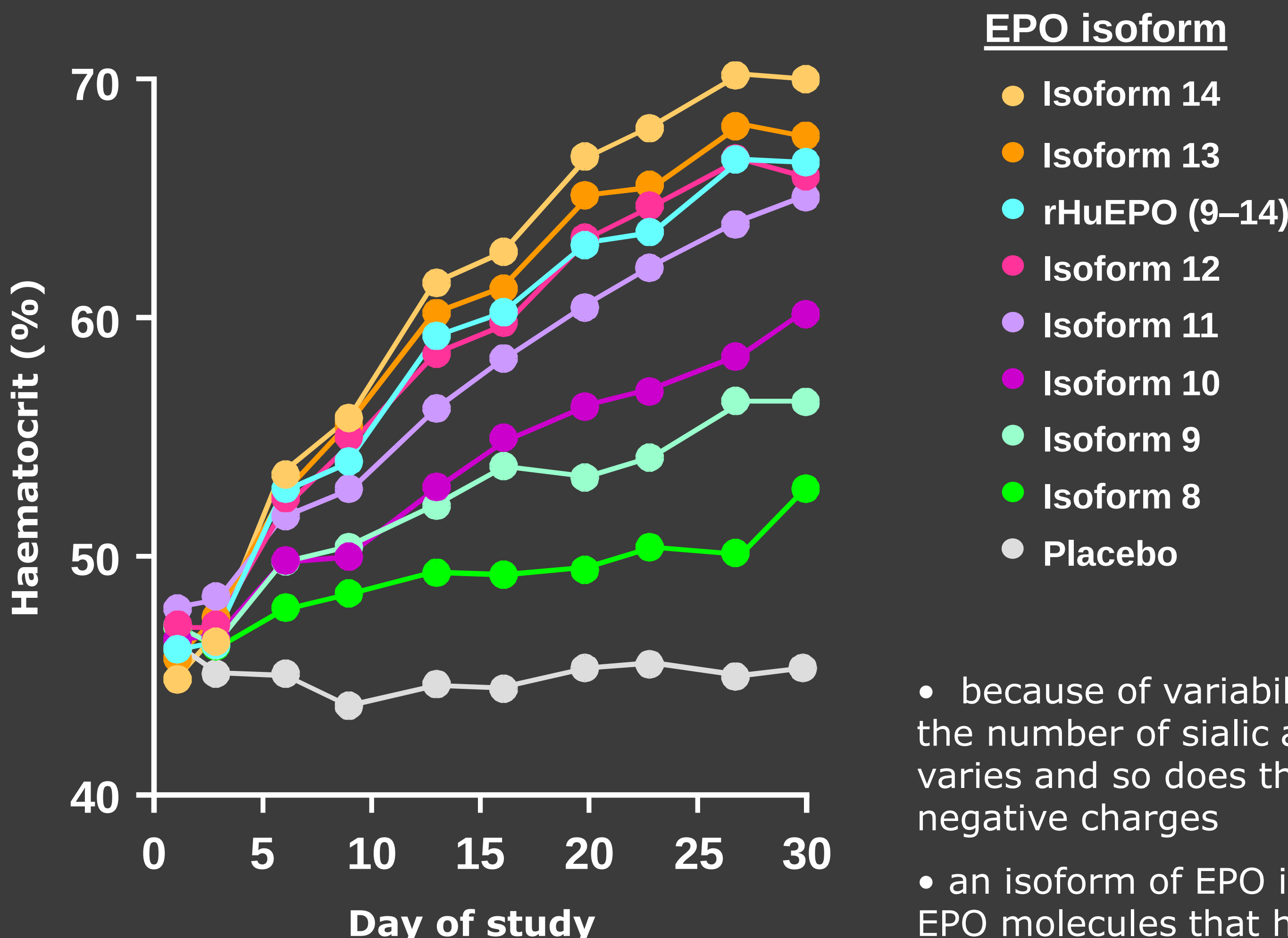


Complexity of the biopharmaceutical epoetin alfa

- Natural human erythropoietin is a hormone
- Recombinant human erythropoietin (e.g. epoetin alfa) is identical
- Epoetin consists of several different forms
- These forms have different biological properties



In-vivo activity in mice



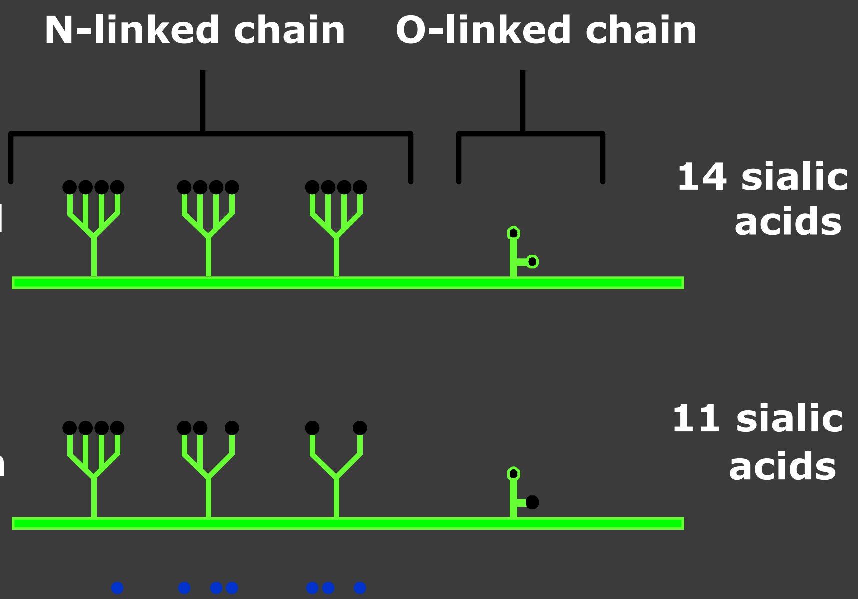
- because of variability in sugar structure, the number of sialic acid molecules on EPO varies and so does the molecule’s net negative charges
- an isoform of EPO is defined as a subset of EPO molecules that has a defined charges due to its sialic acid content
- EPO alfa has been purified so as to contain isoforms 9-14

Egrie JC et al. ***Glycoconj J.*** **1993;10:263**

Significance of carbohydrate content

in-vivo activity increases with increasing sialic acid content

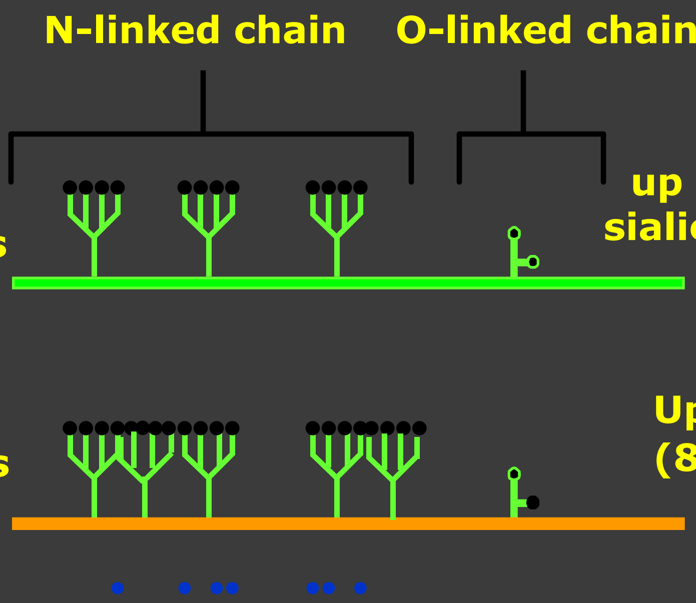
r-HuEPO has a theoretical maximum of 14 sialic acids



Hypothesis: adding carbohydrate (sialic acid) beyond maximum would enhance in-vivo activity

Egrie JC, Browne JK. *Nephrol Dial Transplant*. 2001;16(suppl 3):3-13

Significance of carbohydrate content



Three N-linked carbohydrate chains

up to 14 sialic acids

r-HuEPO:

- 30,400 daltons
- 40% carbohydrate

Five N-linked carbohydrate chains

Up to 22-sialic acid (8 additional residues)

darbepoetin:

- 37,100 daltons
- 51% carbohydrate

Egrie JC, Browne JK. *Nephrol Dial Transplant*. 2001;16(suppl 3):3-13

- At present six different ESAs are available:

- Epoetin alpha,
- Epoetin beta,
- Epoetin omega,
- Epoetin delta,
- Darbepoetin alpha,and
- Continuous Erythropoietin Receptor Activator(CERA)

Darbepoetin alpha

- **Darbepoetin alpha is an ESA with prolonged half-life.**
- **As in epoetin alpha and beta, it is produced in Chinese hamster ovary cells but it differs from EPO in the amino acid sequence at five positions allowing the adding of two extra N-linked carbohydrate chains.** *Ala30Asn, His32Thr, Pro87Val, Trp88Asn and Pro90Thr* **.**

- **These molecular changes result in:**
  - Longer circulating half-life (25 h when given intravenously and 48 h by the subcutaneous route)
  - 4.3-fold lower relative affinity for the EPO receptor.
  - The drug can remain at room temperature (up to 25C) for a maximum single period of 7 days.

CERA

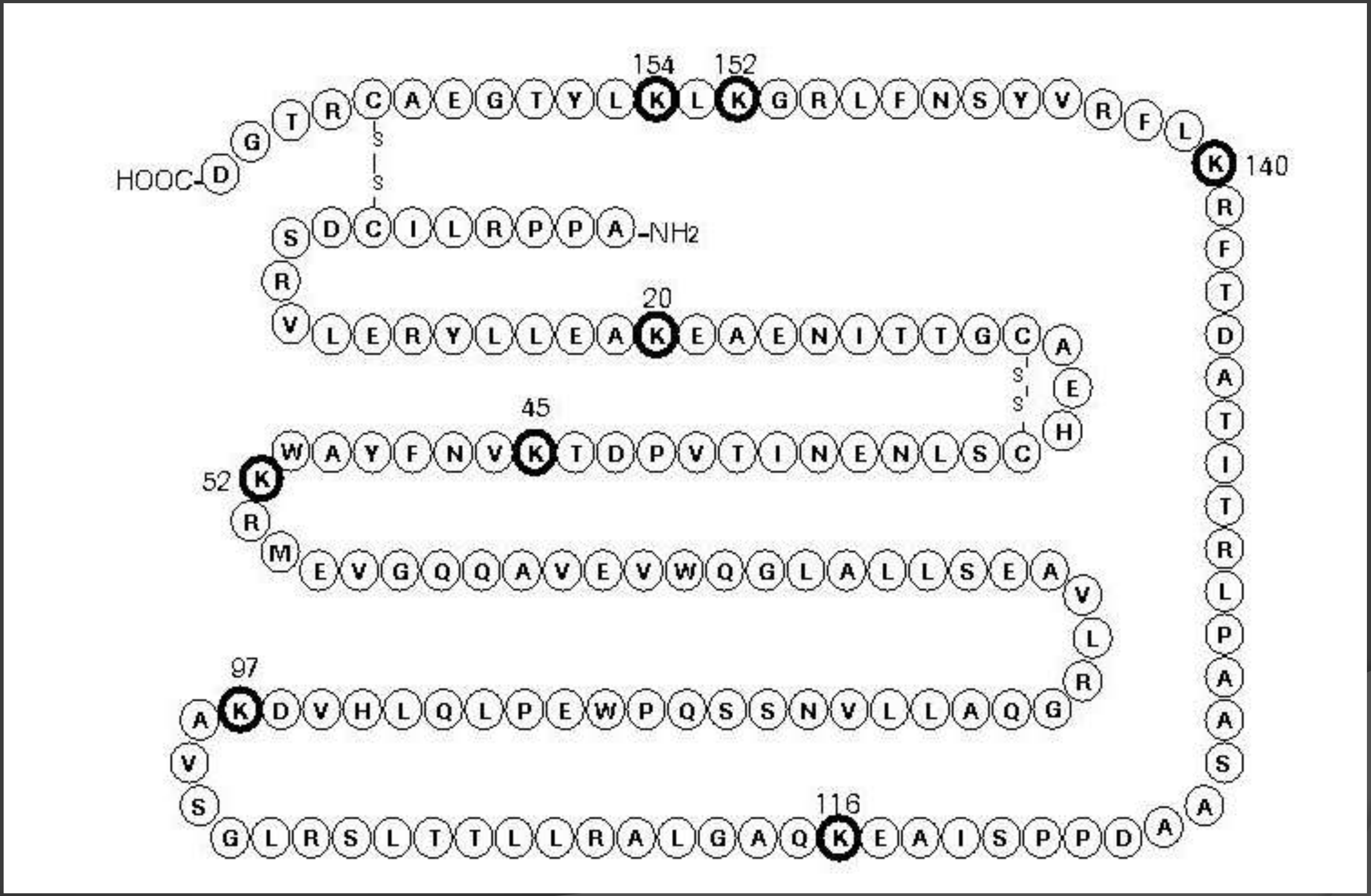
- Is another ESA that is obtained by adding a large water-soluble polyethylene glycol moiety to the EPO beta molecule.
- This agent has:

-a much higher molecular weight than that of EPO (60,000 Da vs 34,000 Da)

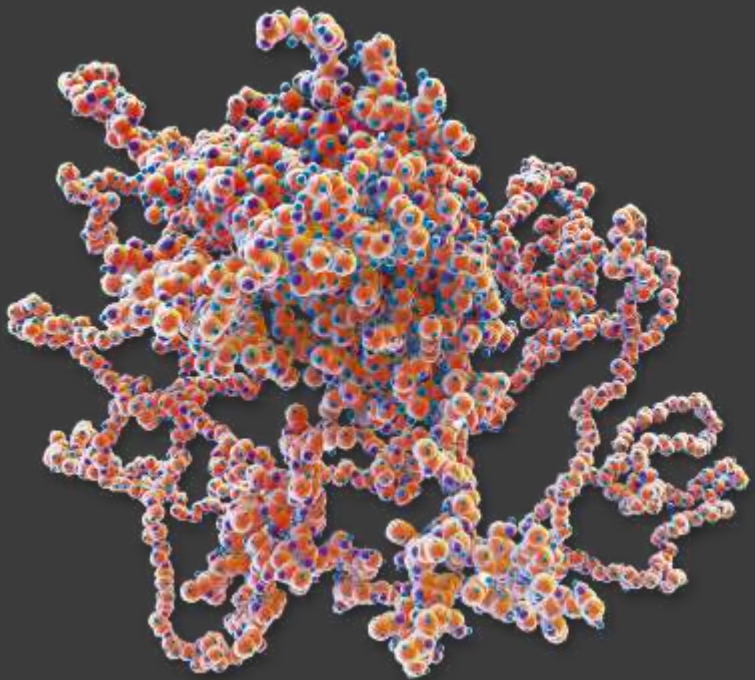
-and a longer half-life (130 h when administered either intravenously or subcutaneously).

-Moreover, it has a reduced binding affinity for the EPO receptor, which is 45-fold lower than that of epoetin beta, mainly because of a much slower association rate.

CERA



CERA

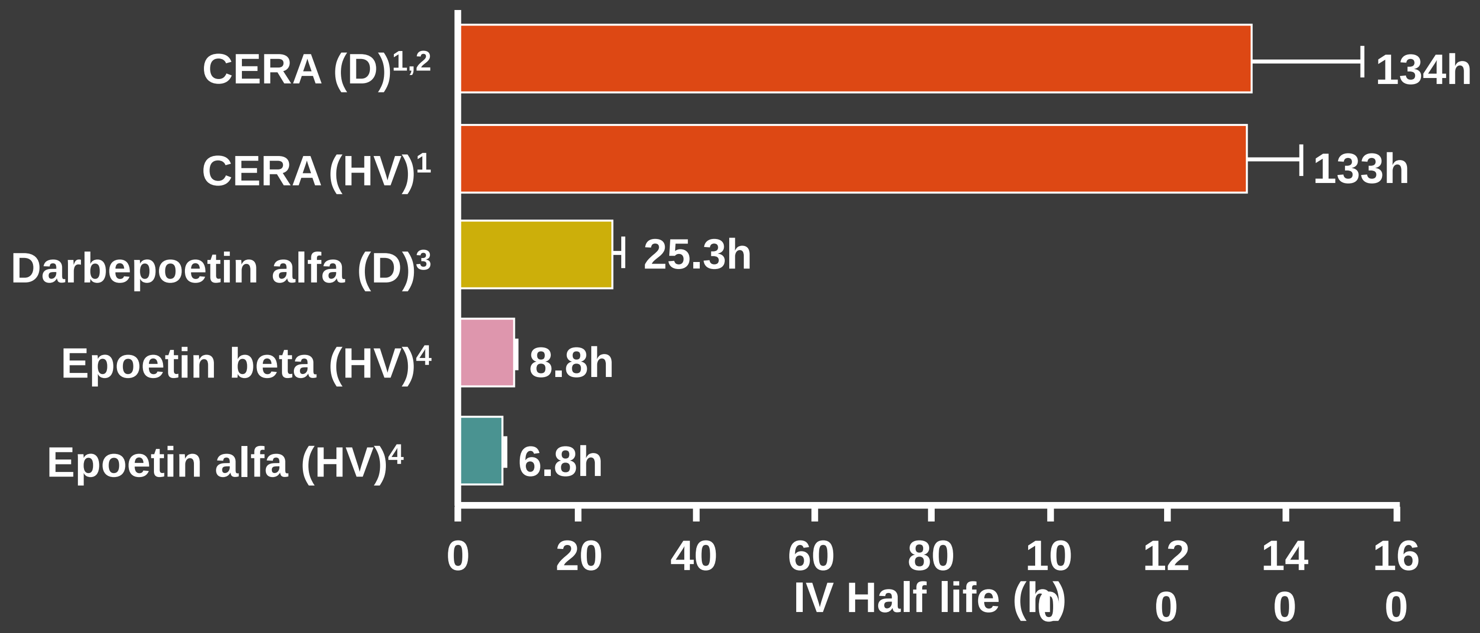


Molecular mass ~60 000 Da

- C.E.R.A., a continuous erythropoietin receptor activator for treatment of anaemia
- integration of amide bonds between amino groups on N-terminus or lysine residues and methoxy-polyethylene glycol-butanoic acid

Macdougall et al. ASN 2003

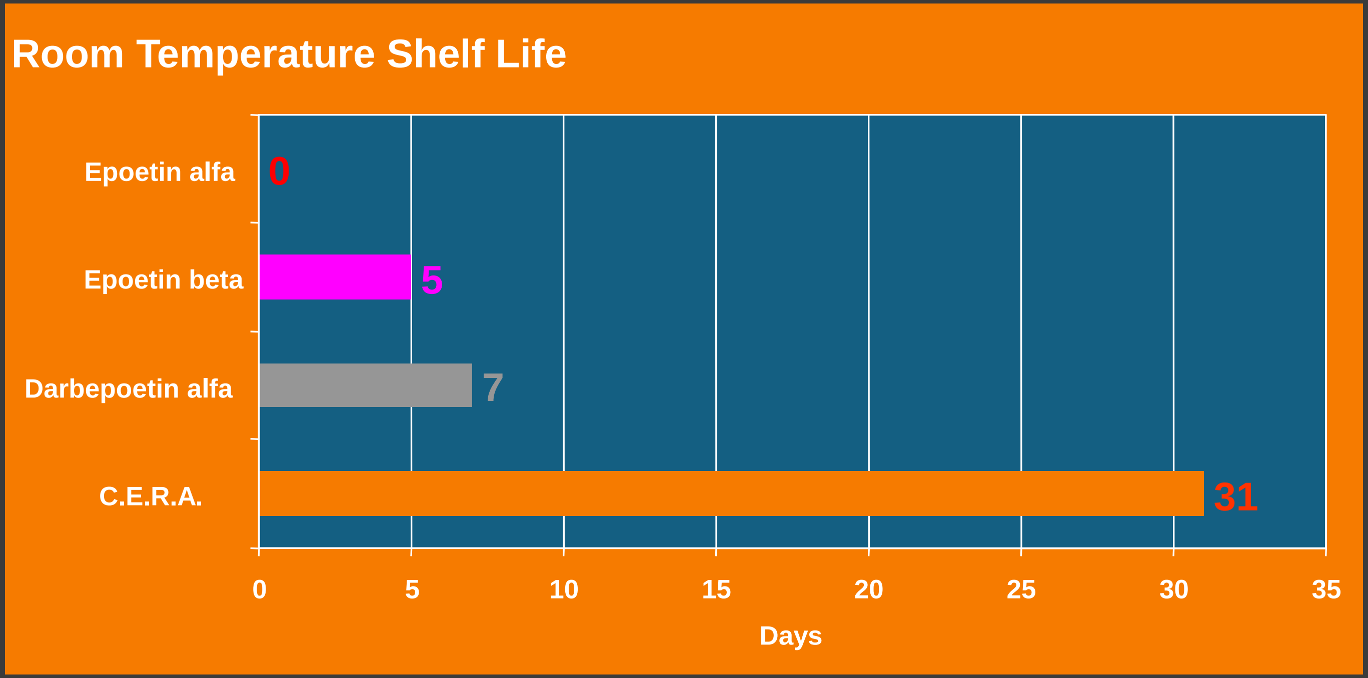
Half-life of ESAs



D, dialysis patients; HV, healthy volunteers;
h, hours, IV, intravenous; SC, subcutaneous

[1]Macdougall et al. Clin J Am Soc Nephrol. 2006;1:1211-1215;
[2]Macdougall et al. J Am Soc Nephrol. 2005; 16:759A;
[3]Macdougall et al. J Am Soc Nephrol. 1999;10:2392-2395;
[4]Halstenson et al. Clin Pharmacol Ther. 1991;50:702-712

Refrigeration



Reduce risk of spoiled product due to interruption of cooling chain

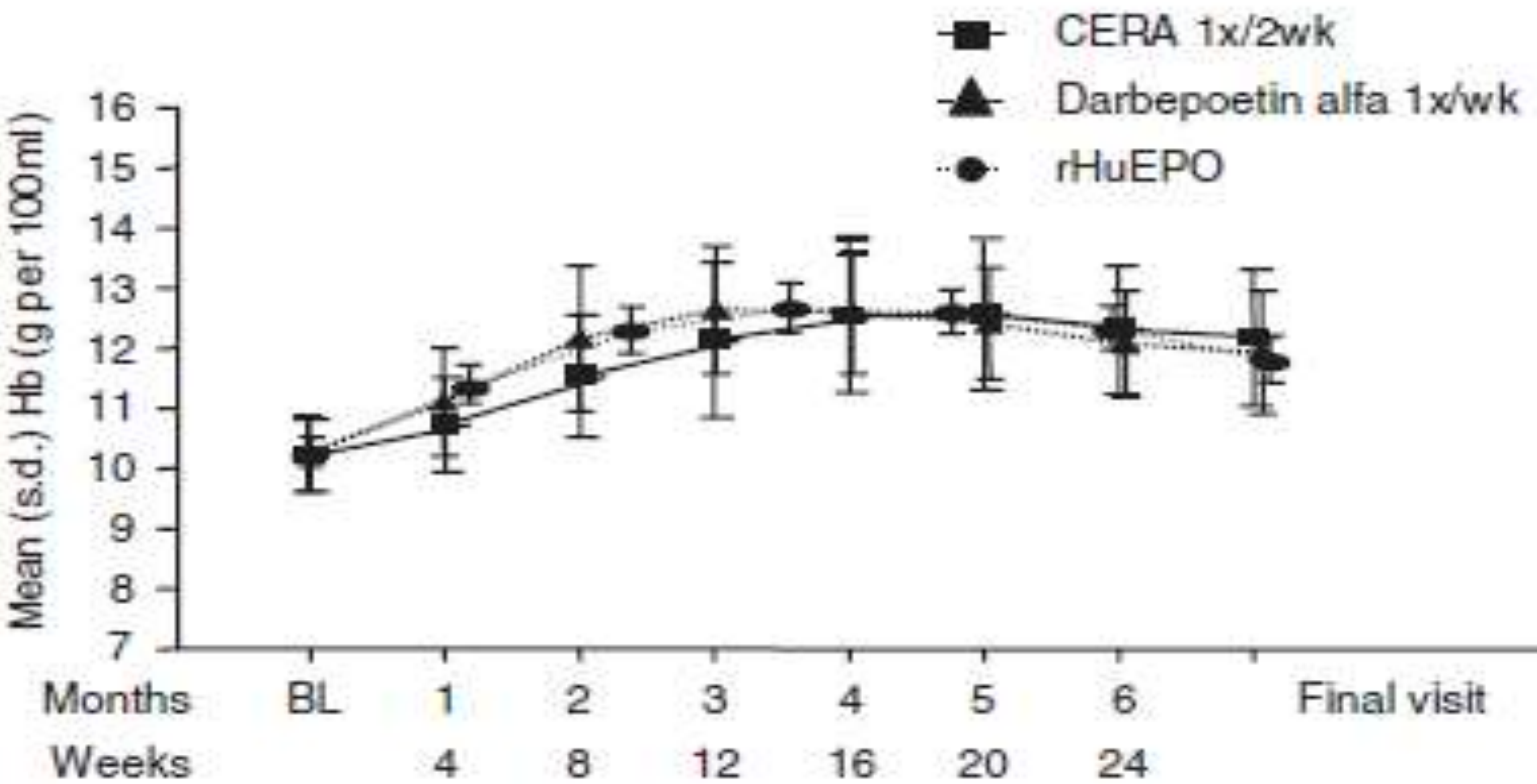


Figure 1 | Hb concentrations during correction phase with CERA, rHuEPO, and darbepoetin alpha in EPO-naive CKD patients not on dialysis. The observed raise in Hb concentration is smothering with CERA than with other ESAs. Data are obtained from reference Macdougall *et al.*[21] and from reference Locatelli *et al.*[13] CERA, continuous erythropoiesis receptor activator; CKD,

Indications of ESAs

- Anemia of CKD.
- Anemia of cancer patient (non myeloid malignancy).
- Anemia of related to therapy with zidovudin for HIV infection .
- Reduction of allogenic blood transfusion in surgery patient (elective, non-cardiac, non vascular).

Anaemia Management Guidelines and Target Hb

ERBP 2010
11-12 g/dL

DOQI
11-12 g/dL

EBPG
>11 g/dL
(upper limit not defined)

KDOQI
11-12 g/dL

EBPG
>11 g/dL
(upper limit individualised)

KDOQI
≥11 g/dL
(caution >13 g/dL)

KDOQI
2007 update
11-12 g/dL
(not intentionally >13 g/dL)

1997 | 1998 | 1999 | 2000 | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2010

CSN
11-12 g/dL

CARI
11-12 g/dL CVD
12-14 g/dL no CVD

UK RA
>10 g/dL

CARI
>11 g/dL CVD
12-14 g/dL no CVD

UK NICE
10.5-12.5 g/dL
10-12 g/dL in children <2yr

CARI
11-12 g/dL CVD
12-14 g/dL no CVD

CVD=cardiovascular disease EBPG=European Best Practice Guidelines
CSN=Canadian Society Nephrology NICE=National Intitute of Health&Clinical excellance
CARI=Caring for Australian with Renal Impairment

European Best Practice Guidelines

Recommendation

The optimal target Hb concentration may vary in patients with co-morbidity or "non-standard" causes of renal failure

- Hb > 11 -12 g / dl are not recommended for patients with sever cardiovascular disease (class II of NYHA classification) unless continuing severe symptoms dictate otherwise
- Until data become available, patients with diabetes should be maintained at a Hb of 11 -12 g / dl
- Patients with chronic hypoxaemic pulmonary disease
- Patients with sickle celle disease (homozygotes) -> Hb of 7-9 g/dl

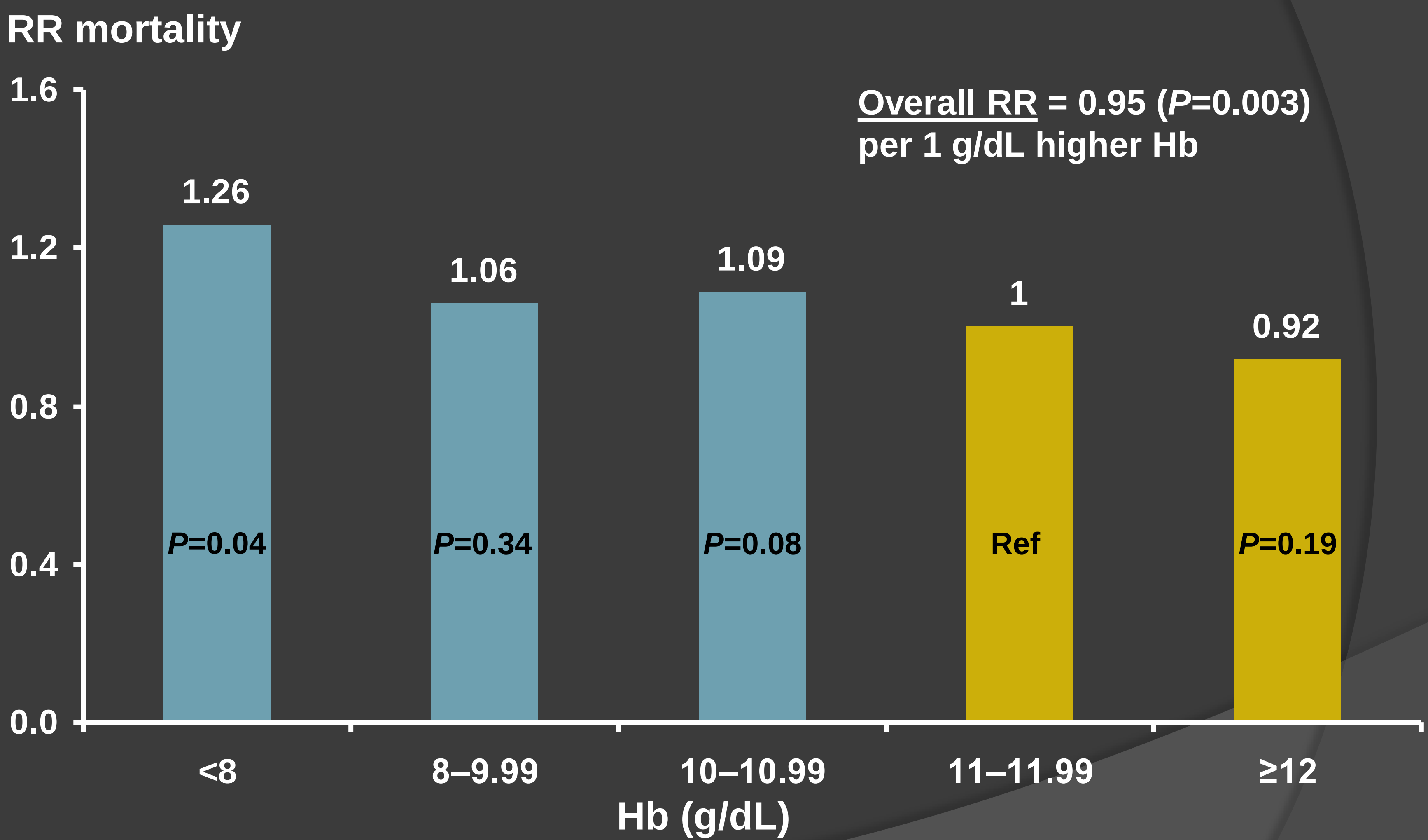
Locatelli et al. Nephrol Dial Transpl 2004; 19,suppl 2

Hb target ranges – the evidence

Sources:-

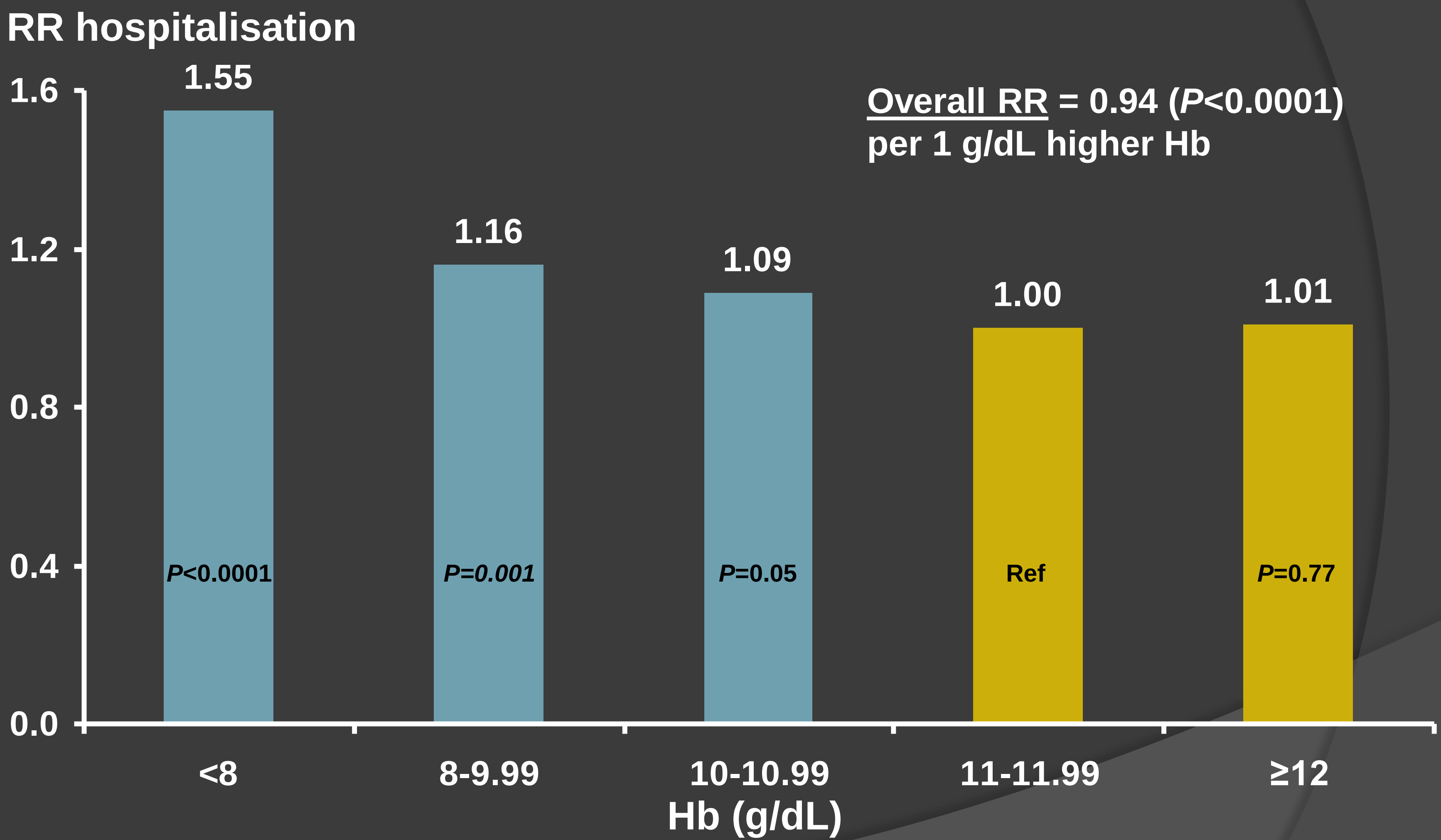
- **Lancet meta-analysis**
- **Latest ERBP Anemia Guidelines update**

Mortality Risk Increases with Hb <11 g/dL



Pisoni et al. Am J Kidney Dis. 2004;44:94-111
Locatelli et al. Am J Kidney Dis. 2004;44(Suppl 3):27-33

Hospitalisation Risk Increases with Hb <11 g/dL



Pisoni et al. Am J Kidney Dis. 2004;44:94-111
Locatelli et al. Am J Kidney Dis. 2004;44(Suppl 3):27-33

How to Initiate ESA Therapy

Agent	Recommended Dose
Epoetin	50-100 units/kg administered either IV or SC, 3 times per week[1,2]
Darbepoetin alpha	0.45 μg/kg, administered as a single IV or SC injection once weekly[5]
C.E.R.A.	0.6 μg/kg administered as a single IV or SC injection once every 2 weeks[8]

IV=intravenous; SC=subcutaneous.

1.Epogen® (epoetin alfa) prescribing information, Amgen, Inc, Thousand Oaks, Calif.; 2. Procrit® (epoetin alfa) prescribing information, Ortho Biotech Products, L.P., Raritan, New Jersey. 3. Provenzano R, et al. *Clin Nephrol*. 2005;64:113-123; 4. Provenzano R, et al. *Clin Nephrol*. 2004;61:392-405. 5. Aranesp® (darbopoetin alfa) prescribing information, Amgen, Inc., Thousand Oaks, Calif. 6. Suryani MG, et al. *Am J Kidney Dis*. 2003;23:106-111; 7. Ling B, et al. *Clin Nephrol*. 2005;63:327-334. 8.

ESA Utilization Guidelines

Dose Adjustments

- If Hb increases by $\geq$ 2 gm/dL per 4 weeks and/or Hgb level > 12 gm/dL, decrease dose by 20 to 25%
- If Hb level is increasing < 1 gm/dL per 4 weeks, increase dose by 20 to 25%

ESA Utilization Guidelines

Dose Adjustments

20 to 25% dose adjustments may be achieved by:

- Altering the ESA dose
- Altering the time interval between injections

ESA Utilization Guidelines

Dose Adjustments

- Increases in dose should not be made more frequently than once a month.
- Avoid holding doses to avoid marked drop in ESA sensitive RBC precursors.

What If Hb decreses => 2g/dl in 2W

- Assess for iron, Folic acid or Vit B12 defic.
- Infections and Inflammations
- Malignant Process
- Occult blood loss
- Hemolysis
- Aluminium toxicity
- Osteofibrosis cystica
- Evaluate for PRCA(pure Red cell Aplasia)

Monitoring Rate of Hb Response

- It is recommended that the dose of ESA be decreased if the Hb increase exceeds 1.0 g/dL in any 2-week period.
  - In clinical trials, increases in Hb >1.0 g/dL during any 2-week period were associated with increased incidence of:
    - Cardiac arrest
    - Neurologic events (including seizures and stroke)
    - Exacerbations of hypertension
    - Congestive heart failure
    - Vascular thrombosis/ischemia/infarction
    - Acute myocardial infarction
    - Fluid overload/edema

Epogen® (epoetin alfa) prescribing information, Amgen, Inc, Thousand Oaks, Calif.
Procrit® (epoetin alfa) prescribing information, Ortho Biotech Products, L.P., Raritan, New Jersey.
Aranesp® (darbopoetin alfa) prescribing information, Amgen, Inc., Thousand Oaks, Calif.

ESA Utilization Guidelines

Dose Adjustments

More frequent Hb &/or iron indices monitoring may be necessary when:

- Recent bleeding or surgery
- Post hospitalization
- Post IV iron course
- Periods of ESA hypo-response

Epo Resistance

- **Resistance to EPO** has been defined by the National Kidney Foundation **(DOQI) as the failure to achieve target Hb within four to six months following the administration of 450 U/kg/week intravenously or 300 U/kg/week subcutaneously or as the failure to maintain target Hb at that dose.**

(National Kidney Foundation DOQI, 1997).

ESA Utilization Guidelines

HD Patient with ESA Resistance??

- Infection/Inflammation
- Blood Loss, Guiac Positive Stools
- Hyperparathyroidism
- B12, Folate Deficiencies
- Aluminium Intoxications
- Sickle cell, Thalacemias
- Multiple Myeloma/Malignancy
- ACE Inhibitor use

Cycling of Hb in Dialysis Patients

- Cycle defined as oscillation in Hb with amplitude >1.5 g/dL of >8 weeks duration
- Data for 281 hemodialysis patients treated with epoetin between 1998 and 2003 and followed for 1 year :

  Adequate Hb levels (mean 11.8 g/dL) were achieved

  However

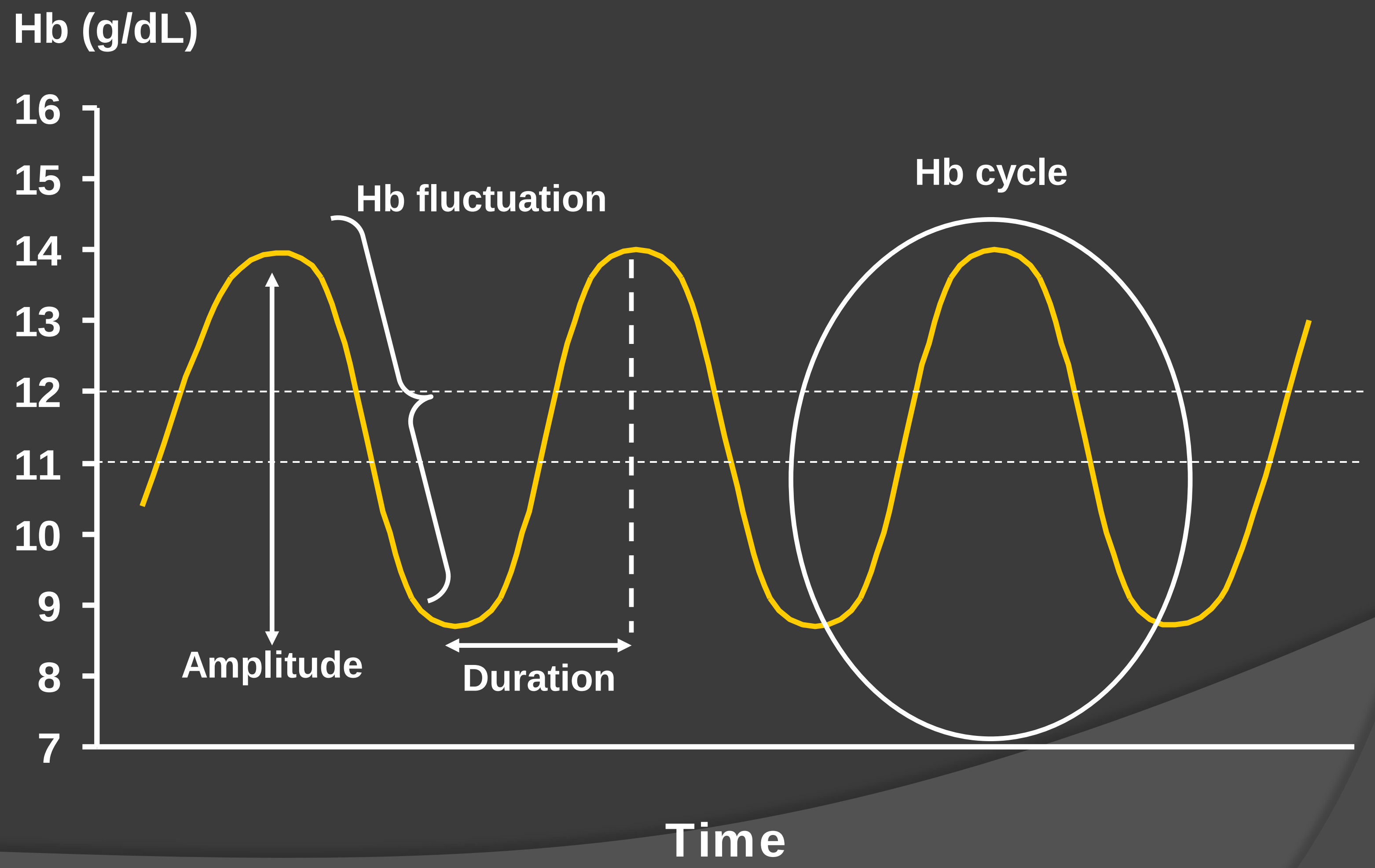
  - >90% patients experienced cycling
  - Patients experienced ~3 excursions † per year
  - Patients required ~6 dose adjustments per year

† defined as ≥1 cycles of amplitude >1.5 g/dL of >4 weeks duration

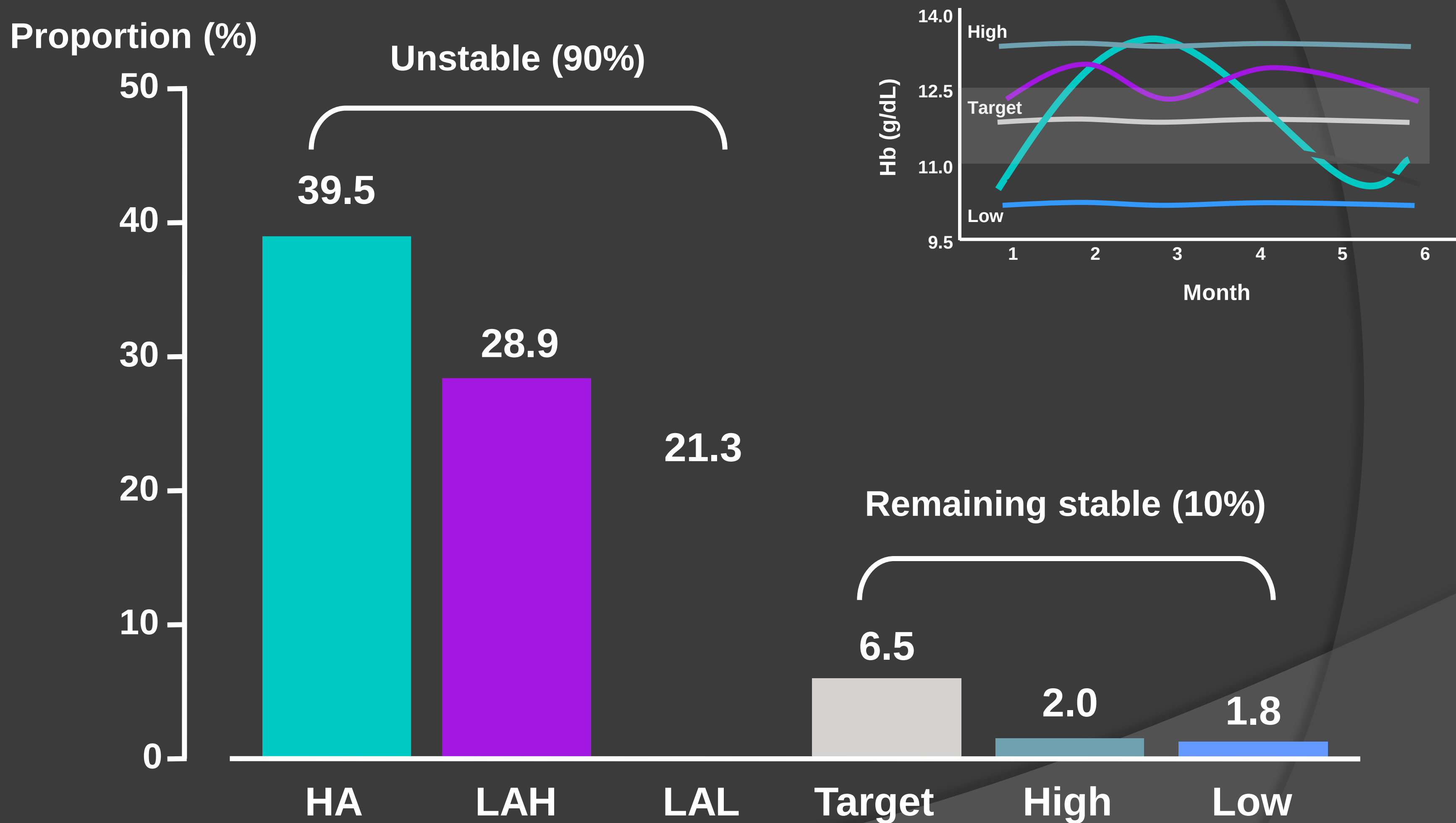
Fishbane & Berns. Kidney Int. 2005;68:1337-1343

Hb Fluctuations Outside Target Range

Model showing Hb fluctuations and cycling



Majority of Patients Experienced Hb Fluctuation Over the 6-Month Period

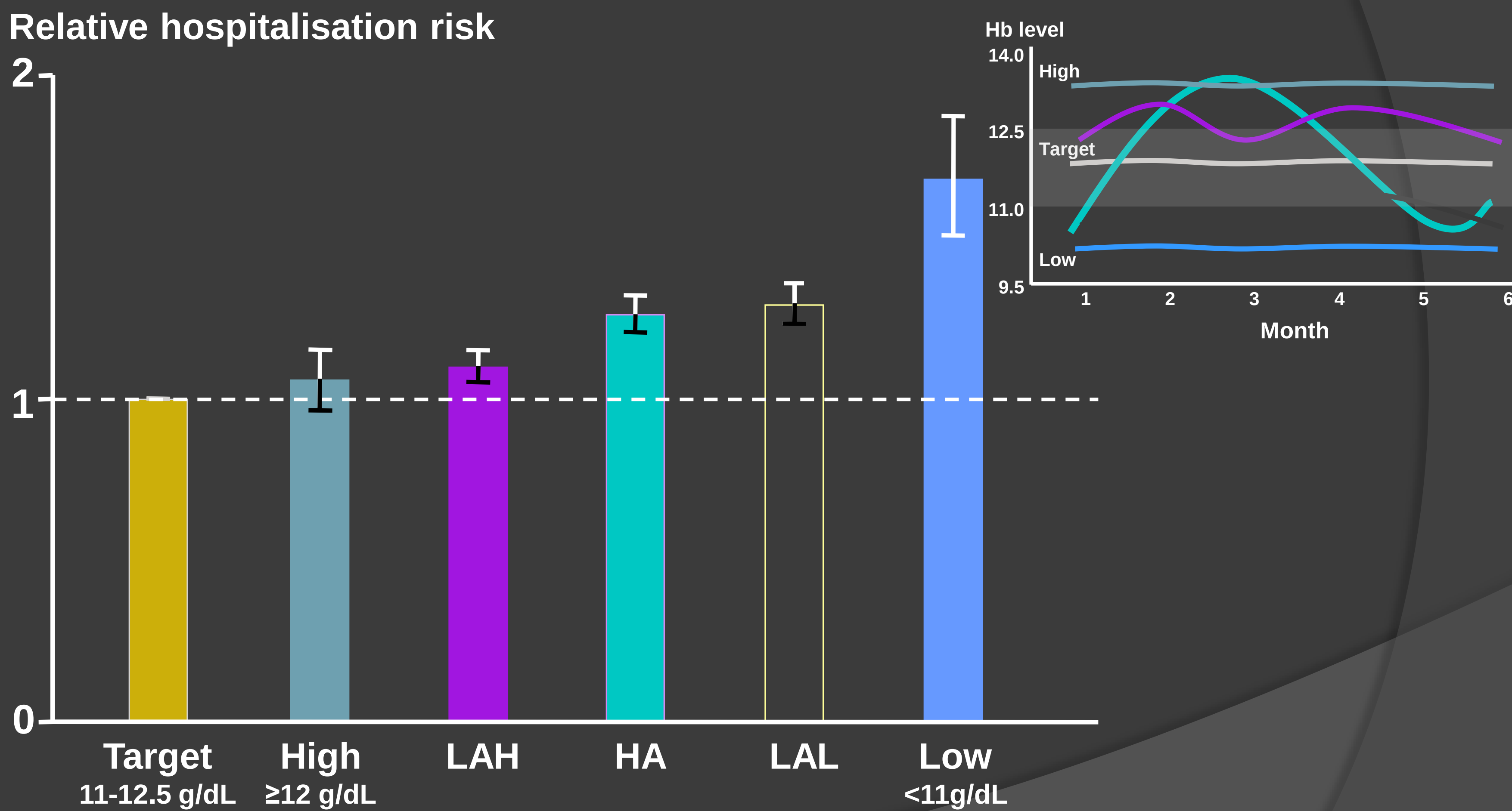


n=152 446 HD patients with Medicare as primary payer and EPO claims in each of the first 6 months of 2003

Adapted from
Ebben J et al. *Clin J Am Soc Nephrol.* 2006;1:1205-1210

Risk of Hospitalisation by Hb Stability Category

Risk is lowest in patients with stable Hb 11-12.5 g/dL

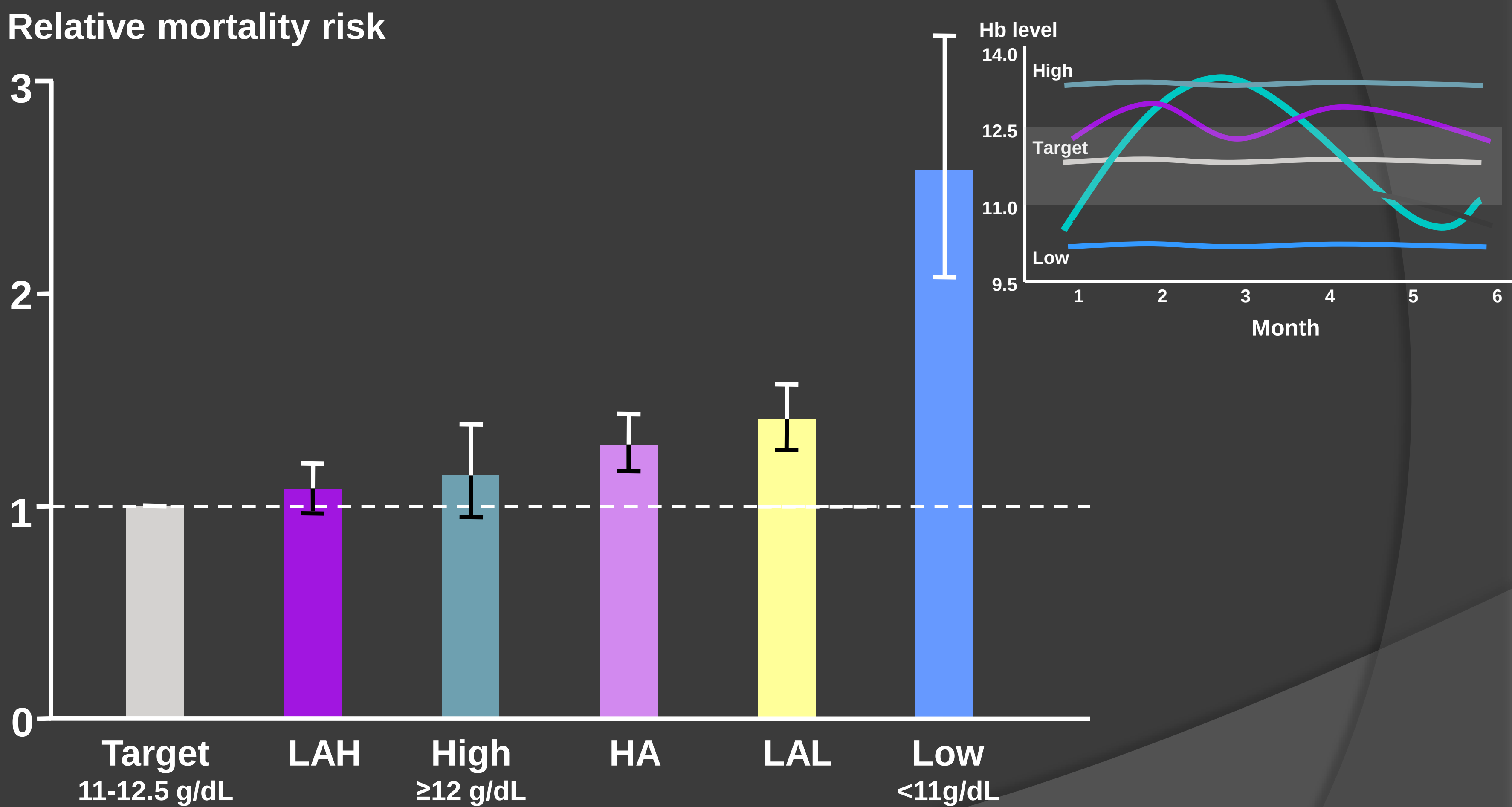


n=152 446 HD patients with Medicare as primary payer and EPO claims in each of the first 6 months of 2003

Adapted from Gilbertson et al. *Nephrol Dial Transplant*. 2006;21(Suppl 4):iv169

Risk of Mortality by Hb Stability Category

Risk is lowest in patients with stable Hb 11-12.5 g/dL



n=152 446 HD patients with Medicare as primary payer and EPO claims in each of the first 6 months of 2003

Adapted from Gilbertson et al. *Nephrol Dial Transplant*. 2006;21(Suppl 4):iv169

New ESA agents

- The Erythropoietin-mimetic peptides. (Hematide)
- Hypoxia inducible factor . (FG -2216)
- Epo Gene transfer.

Melnikova .Nat Rev Drug Discov. 2006;5:627-628

The erythropoietin-mimetic peptides

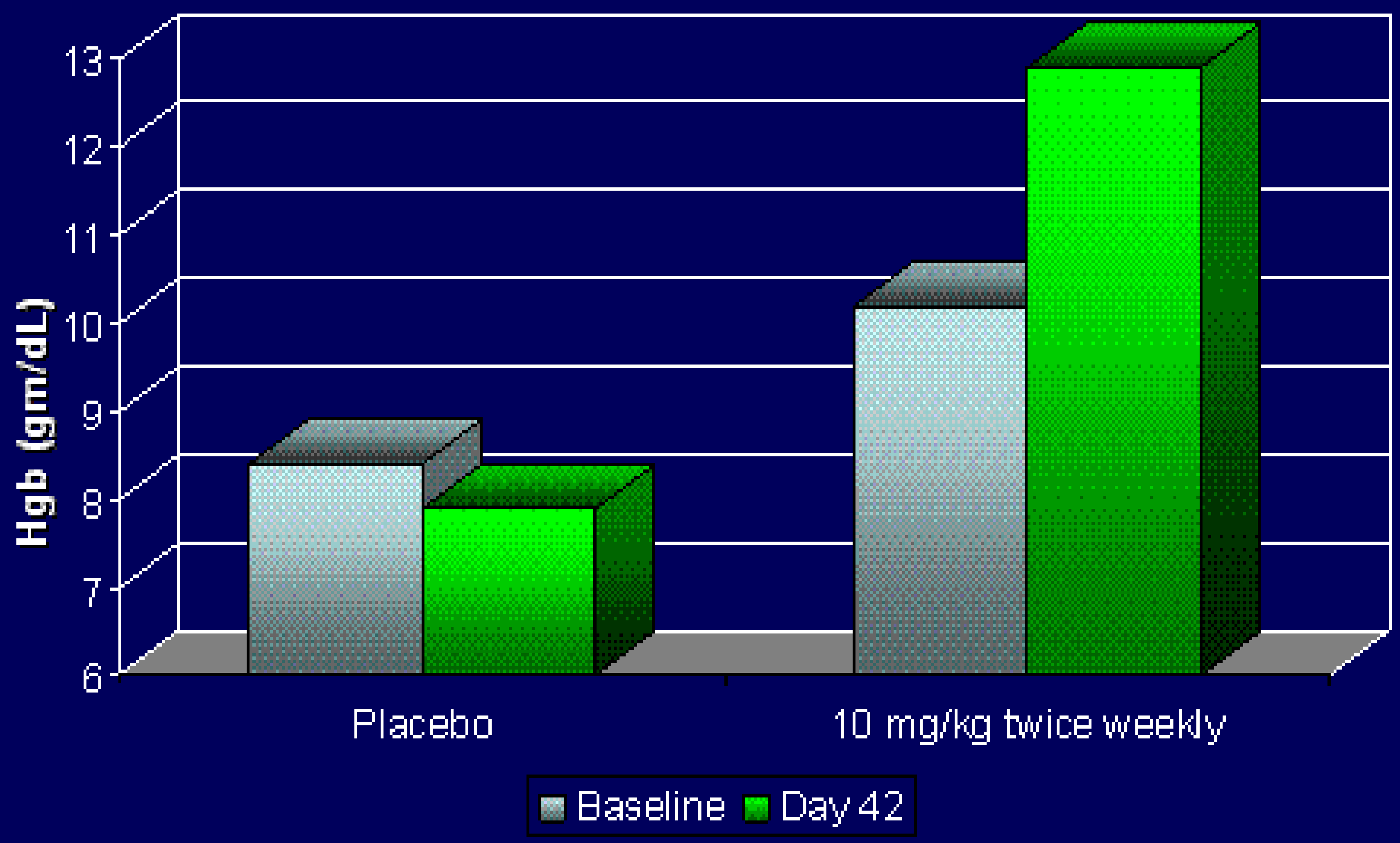
- **One agent in this class: Hematide is a Pegylated,Synthetic dimeric peptide ESA with a novel amino acid sequence unrelated to Erythropietin.**
- **In vitro studies have shown that Hematide binds the EPO receptor.Triggers intracellular signaling, and causes cell proliferation and differentiation**
- **in phase 2 of clinical development.**
- **Single doses of Hematide in randomized,double blind controlled trial caused dose-dependent increases in circulating reticulocytes,Rbcs and Hb.**
- **Antibodies generated to erythropoietin don’t cross react with Hematide**

FG-2216

- Prolyl hydroxylase inhibitor
- Small molecule
- Orally active
- Results in 3 to 5-fold increase in endogenous EPO
- Regulates genes that modulate iron metabolism
  - Downregulates hepcidin
  - Enhances iron transport and recycling
- Modulates inflammatory markers
- 92 subjects treated; no serious drug-related adverse events

Günzler. ASN. 2005.

Hemoglobin Response to FG-2216



Günzler. ASN. 2005.

Preliminary Results from a Randomized, Single-Blind, Placebo-Controlled Trial of FG-4592, a Novel Hypoxia Inducible Factor Prolyl Hydroxylase Inhibitor, in CKD Anemia

PA Frohna, MD, PhD[1], G Kochendoerfer, PhD[1], S Milwee, PharmD[2], J Pinkett, MS[1], T Lee, PhD[1], K Moore-Perry, MS[1], J Chou, PhD[1], RH Ellison, MD[3]

[1]FibroGen, Inc., South San Francisco, CA; [2]Redwood City, CA; [3]New York, NY

ABSTRACT

Background: FG-4592 is an oral inhibitor of hypoxia inducible factor (HIF) prolyl hydroxylase in clinical development for the treatment of anemia. Stabilization of HIF, a cytosolic transcription factor, by FG-4592 leads to activation of the genes associated with erythropoiesis, including EPO and enzymes involved in iron metabolism.

Study Design: A randomized, single-blind, placebo-controlled, 4-week study of oral FG-4592 (1 to 4 mg/kg) given 2 or 3 times weekly. The objectives of this study were to characterize the safety, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of FG-4592 in subjects with CKD anemia. Thirty subjects were to be enrolled into 2 cohorts at each dose: PK (n=12, Hb <13 g/dL) and Treatment (TX, n=18, Hb<11 g/dL). All subjects were monitored for safety, including vital signs, clinical labs, and adverse events during treatment and for 4 weeks thereafter.

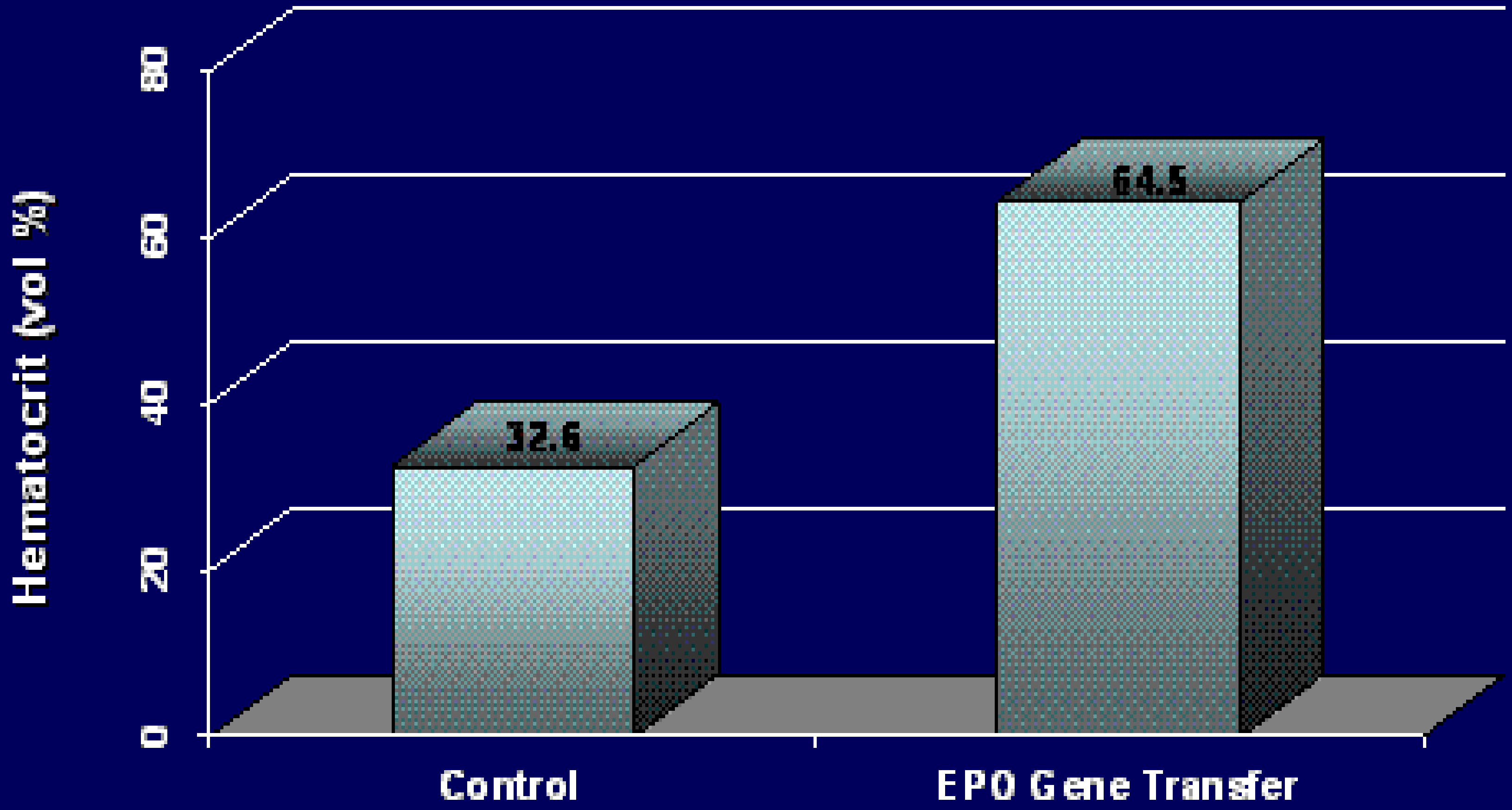
Results: Data from the 1 mg/kg cohort (21 active- and 8 placebo-treated) demonstrate that FG-4592 doses up to 120 mg are considered generally well-tolerated, with treatment emergent AEs attributed to study drug reported from only 2 subjects (1 active and 1 placebo). No clinically significant changes in serum chemistry or vital signs were observed in any subjects. Multiple samples from the PK subjects were collected and used to measure FG-4592 and circulating endogenous EPO levels. FG-4592 was rapidly absorbed with a mean T_{max}=1.8 hrs, mean C_{max}=5.9 mg/mL, and mean half-life=11 hrs, which were comparable after the first and last dose, and similar to those previously observed in healthy subjects. Median peak plasma EPO levels of 115 mIU/mL occurred 8–12 hrs post-dose, and were comparable for first and last dose. In the TX group, 5 of 13 subjects (38%) treated with FG-4592 had increases in Hb >1 g/dL during the 4-week treatment period, and maintained that increase for 2-4 wks after stopping treatment. None of 4 placebo subjects had a similar Hb increase. In conclusion, 4 weeks of treatment with FG-4592 was well-tolerated and produced significant Hb increases in some subjects with CKD anemia.

EPO Gene Transfer

- Wistar rats adenine-induced uremia
- EPO gene transfer
  - plasmid created by inserting rat EPO cDNA into pCAGGS expression vector
  - Intramuscular injection
  - Activated by electrostimulation

Ataka. Am J Nephrol. 2003;23:315-323.

EPO Gene Transfer Wistar Rats



Ataka. Am J Nephrol. 2003;23:315-323.

Minimizing cost of ESAs

1. Correct other causes of anemia .
2. Continue iron supply during ESAs therapy.
3. Do not adjust the dose- except once/ two weeks to be guided by Hb, Hct % and Retic count
4. Follow SC route for administration
5. ESAs doses should never held (practical point)
6. Use adjuvant drugs.
7. Adequate dialysis .
8. Good nutrition

- 3.3.1 L-Carnitine: In the opinion of the Work Group, there is insufficient evidence to recommend the use of L-carnitine in the management of anemia in patients with CKD.

- 3.3.2 Vitamin C: In the opinion of the Work Group, there is insufficient evidence to recommend the use of vitamin C (ascorbate) in the management of anemia in patients with CKD.

Do you encourage androgen?

- 3.3.3 Androgens: Androgens should not be used as an adjuvant to ESA treatment in anemic patients with CKD. (*STRONG RECOMMENDATION*)

Adjuvant therapy updated KDOQI guidelines

Iron supplementation

Target levels of iron parameters

Parameter	Optimal	Acceptable
Ferritin (mg/l)	200-500	100-800
Transferrin saturation (%)	30 - 40	20 - 50
Proportion of hypochromic red cells (%)	<2.5	<10

To be tested every 3 months

Laboratory evaluation of Iron status

I- Serum ferritin & TSAT

S. ferritin (ng/ml)	TSAT %	Clinical situation
<100	<20	Iron Deficiency anemia
100-500	20-30	Normal Iron status
>500	>50	Iron overload
>100	<20	Functional iron deficiency anaemia

Neither very accurate .

Practical Considerations For More Accurate Evaluation Of These Tests

- Morning venous sample
- Sample should be checked for s. ferritin, TSAT & CRP.
- One week after last IV iron therapy .
- Done by the same lab, same technique even the same technician.
- Before ESAs therapy.
- Re-evaluated every 3 mouths together with peripheral hypochromic RBCs.

Laboratory evaluation of Iron status

2- Reticulocyte Hb concentration :

- Most stable , good level of diagnostic accuracy, and cost effectiveness .
- Direct measure of iron availability of at the level of erythron.
- Value <29-32 pg → iron deficiency anemia and IV iron therapy should be initiated.

Laboratory evaluation of iron status

3- Other tests :

- Soluble transferrin receptors.
- Bone marrow iron (most accurate).
- % of hypochromic RBc in the peripheral blood
- Zinc protoporphyrin.

Adverse effects of ESA therapy

- Worsening of HTN.
- Seizure
- Increased blood clotting
- Slight decrease of Kt / V
- Impaired phosphorus balance
- Hyperkalaemia.
- Expensive.
- Pure Red cell aplasia (PRCA).

Contraindications of ESAs

- Uncontrolled HTN.
- Known hypersensitivity to mammalian cell –derived products.
- Know hypersensitivity to human albumin .
- Children (not established).
- History of :
  - Seizure .
  - Haematologic disorder (sickle cell anamia, myelodysplastic disorder, hypercoagulable state).

Cardiovascular and Non-Cardiovascular Benefits of Anaemia Correction

Cardiovascular

- ↓ Cardiac output
- ↓ Left ventricular hypertrophy
- ↓ Left ventricular index*
- ↓ Stroke volume
- ↓ Incidence of coronary artery disease

Non- Cardiovascular

- ↓ Fatigue
- ↑ Working capacity
- ↑ Exercise tolerance
- ↑ Blood viscosity
- ↑ Cognitive ability
- ↓ Lipid profile
- ↑ Sexual function


Thank You
Designed by zahra2 sob7